Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

plasma of WT mice was exactly correlated with the presence of NIPs. HtrA1 and NIP were significantly decreased in HTRA1$^{-/-}$ pups. It is important to note that they showed for the first time that the neonatal NET inhibition system is conserved in humans and mice. Finally, in a preclinical model of neonatal sepsis, inhibition of NETs by treatments with A1ATM$_{383}$S-CF increased survival of WT and HTRA1$^{-/-}$ pups, which was unexpectedly higher in HTRA1$^{-/-}$ pups than in WT pups. From this study, it seems that excess NET formation actually worsens neonatal sepsis. A1AT, a member of the serine protease inhibitors superfamily (SERPINs), is an important inhibitor of NE. The cleavage of A1AT by HtrA1 after Met-382, which is in the middle of the reactive center loop (RCL; aa 368-392) of A1AT, results in a loss of its inhibitory function against NE.[6] It is an interesting possibility that HtrA1 regulates inflammation by balancing 2 opposing functions: downregulation by inhibiting NETs and upregulation by activating NE (see figure). This complicated mode of regulation of neutrophil functions by HtrA1 may explain why both elevations and reductions in HtrA1 levels cause a variety of human diseases.[7]

NET formation is detected in the intervillous space, a maternal-fetal interspace, even in placentas of normal pregnancies; however, it is dramatically increased in the placentas of pregnancies with PE.[3] Dysregulated HtrA1 expression in placenta and in maternal plasma has repeatedly been reported in abnormal pregnancies, for example, PE and intrauterine growth restriction (IUGR).[8] One of the subsequent important issues is whether placental HtrA1 inhibits dysregulated excess NET formation to maintain immune tolerance at the maternal-fetal interface and prevents abnormal placentation and gestation leading to PE-IUGR (see figure).

HtrA1 is a member of HtrA family proteins that are distributed in a range of species from bacteria, yeast, and plants to humans.[7,9] Bacterial HtrAs are heat shock proteins that degrade or refold proteins that are denatured or unfolded under different stress conditions. Mammalian HtrA1 expression is also induced by several stresses, including oxidative stress and endoplasmic reticulum stress. In humans, loss-of-function mutation of the HtrA1 gene is the cause of the hereditary small vessel disease, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy.[10] Furthermore, abnormal expression and activity of HtrA1 are related to various inflammatory diseases, such as age-related macular degeneration, rheumatoid arthritis, osteoarthritis, Alzheimer's disease, and cancer.[7] Another important issue is if and how NET formation regulated by HtrA1 is involved in the pathogenesis of these HtrA1-related diseases (see figure). Certainly, this article will spur additional work on the regulation of NETs.

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PLATELETS AND THROMBOPOIESIS

Comment on Uzun et al, page 992

Cooling down VITT with IVIG

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In this issue of *Blood*, Uzun et al report additional clinical experience using IV immunoglobulin (IVIG) for the treatment of COVID-19 vaccine–induced immune thrombotic thrombocytopenia (VITT).[1]

The COVID-19 pandemic is keeping hematologists busy. From COVID-19 coagulopathy to prevention of COVID-19–associated thrombosis to treatment of hematological complications of COVID-19 vaccines, the pandemic has presented a series of mechanistic, clinical, and therapeutic challenges. The latest hematological COVID-19 conundrum is VITT, a rare prothrombotic complication of certain COVID-19 vaccines. VITT has been reported in patients who received the ChAdOx1 nCOV-19 (AstraZeneca/University of Oxford) or Ad26.COV2.S (Johnson & Johnson/Janssen) vaccines.[2-5] Alternative names proposed for VITT include vaccine-induced prothrombotic immune thrombocytopenia and thrombosis with thrombocytopenia syndrome. VITT should not be confused with immune thrombocytopenic purpura, an uncommon but well-recognized complication of many vaccines, including the COVID-19 vaccines.

The clinical presentation of VITT resembles that of heparin-induced

thrombocytopenia (HIT), particularly the spontaneous or autoimmune form of HIT that can occur in the absence of heparin administration and is associated with disseminated intravascular coagulation.[6] In both HIT and VITT, patients present with arterial or venous thrombosis in the setting of thrombocytopenia, elevated D-dimer, and high-titer immunoglobulin G (IgG) antibodies that recognize platelet factor 4 (PF4). Some but not all clinical immunoassays designed to detect antiheparin/anti-PF4 antibodies also detect anti-PF4 antibodies in patients with VITT.[7] In many of the cases reported so far, VITT has been associated with thrombosis in unusual sites, such as the cerebral venous sinuses or splanchnic veins.[2-5]

The mechanism of thrombosis in VITT is incompletely understood, but several groups have demonstrated that serum or IgG from patients with VITT causes platelet activation in the presence of PF4, likely by crosslinking Fcγ receptor IIA (FcγRIIA; CD32A) on the platelet surface.[3] A similar mechanism of platelet activation via FcγRIIA occurs in HIT.[6] IVIG can block platelet activation by anti-PF4 antibodies, presumably by competing for binding to FcγRIIA. Because high-dose IVIG has been used successfully to treat autoimmune HIT,[6] preliminary guidance for the treatment of VITT has included the use of IVIG in addition to a nonheparin anticoagulant.[8]

Uzun et al report their clinical and laboratory experience with the use of IVIG in the management of 5 patients who presented with VITT 7 to 9 days after immunization with the ChAdOx1 nCOV-19 vaccine. In addition to high-dose IVIG (1 g/kg body weight daily for 2-3 days), the patients also received a nonheparin anticoagulant (argatroban, dabigatran, or apixaban). An increase in platelet count within 3 days of IVIG administration was observed in all patients, and 4 of 5 patients remained free of new thrombotic events (1 patient experienced progression of cerebral venous sinus thrombosis 6 days after receiving IVIG). In laboratory platelet activation assays, the ability of patient sera to generate procoagulant platelets decreased after treatment with IVIG in 3 of 4 patients tested. Interestingly, the sample without improvement after IVIG administration was from the patient who experienced progression of thrombosis. This observation raises the question of whether specific inhibitors of FcγRIIA might be more effective than IVIG in preventing thrombosis.[9]

The observations of Uzun et al add to a small but growing body of experience supporting the use of IVIG in the clinical management of VITT. Limitations of this study include its small size and retrospective design, the lack of a control group of VITT patients who did not receive IVIG, and the relatively short follow-up period. The duration of prothrombotic risk with VITT is not known, but some patients (including 1 patient reported by Uzun et al) have experienced recurrent thrombosis after an initial improvement in platelet count. Anti-PF4 antibodies are likely to persist for weeks to months, and it is not known whether repeated dosing with IVIG or prolonged treatment with corticosteroids or other immunosuppressive drugs might decrease the risk of recurrent thrombosis. IVIG may also have beneficial effects unrelated to platelet FcγRIIA blockade, possibly via anti-idiotype effects, blocking the neonatal FcR or cooling down inflammation through its interactions with other FcγRs.

Given the low incidence of VITT, it is unlikely that large randomized controlled trials will be conducted to prospectively define its optimal treatment. It seems more likely that hematologists will learn to diagnose and manage these patients by sharing careful clinical and laboratory observations, much the same way we learned to manage HIT from the astute and pioneering observations of Kelton, Warkentin, and Greinacher, among others.[6]

Several other questions about VITT remain unanswered. How does vaccination trigger the formation of anti-PF4 antibodies? Why does it occur after vaccination with adenoviral vector–based COVID-19 vaccines and not messenger RNA vaccines? Why is it more prevalent in women than men? Is thrombosis caused by FcγRIIA-driven platelet activation and/or other mechanisms? What explains the unusual predilection for cerebral venous sinus thrombosis? These questions will continue to keep hematologists busy for some time.

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